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# Promising hepatorenal protective effects of pumpkin (Cucurbita pepo L.) And watermelon (Citrullus lanatus L.) Seed oils against diazinon-induced acute toxicity in rats



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**Abstract**

Aim: The present study aimed to evaluate the toxicity of DZN in the liver and kidney. We also tested the protective effect of pumpkin seed oil (PSO) and/or watermelon seed oil (WSO) against diazinon toxicity.

Material and Methods: Fifty adult male Sprague–Dawley rats were classified into five groups: G1 [control]; G2 [DZN-50 mg/kg b.w]; G3 [DZN + PSO (1.5 ml/kg b.w)]: G4 [DZN + WSO (1.5 ml/kg b.w), and G5 [ DZN + PSO+ WSO].

Results: Diazinon toxicity altered serum kidney and liver function biomarkers. These effects were pronouncedly alleviated by treatment with PSO and WSO.

Discussion: PSO and WSO have a protective role against nephrotoxicity and hepatotoxicity induced by diazinon. PSO was more effective in reducing DZN nephrotoxicity, while WSO was more potent than PSO in reducing DZN hepatoxicity. Moreover, the antioxidant properties of these oils support the bioactive roles of their protective effects on DZN toxicity. This study, therefore, suggests that these oils could be used as preventive factors against the toxicity of DZN due to its antioxidant properties.

**Keywords**

Pumpkin Seed Oil, Watermelon Seed Oil, Diazinon, Hepatotoxicity, Nephrotoxicity

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## Introduction

Organophosphorus compounds are one of the most common types of organic pollutants found in the environment [1]. Toxicities of organophosphorous insecticides cause adverse effects on many organs. Systems that could be affected by organophosphorus insecticides are the nervous system, immune system, liver, muscles, urinary system, reproductive system, and hematological system [2].

Diazinon (DZN) is an organophosphorus insecticide that is widely and effectively used throughout the world with applications in agriculture and cultivation for controlling insects in crops and other food products [3]. Several investigations have shown that DZN was capable of inducing biochemical and physiological alterations [4].

In recent years, interest has increased in using natural products for pharmacological purposes as a form of complementary or replacement therapy [5]. The pumpkin (Cucurbita Pepo L.) is a common conventional food in many countries. Pumpkin seeds contain about 42 to 54% oil. Pumpkin seed oil contains fatty acids (mainly linoleic acid, oleic acid, palmitic acid, and stearic acid). It has high amounts of antioxidant vitamins such as α- and γ-tocopherol, β carotene, and vitamin E. Pumpkin seed oil also contains phenolic compounds such as vanillic acid and vanillin and high levels of selenium and lutein. In comparison to other seed oils, PSO is rich in squalene, which is a carbon organic compound that has many commercial uses. It is an affluent source of phytosterols and proteins [6]. The presence of all these constituents in pumpkin seed oil clarifies their useful and valuable effects on human health. Nowadays, it is used in the treatment of many diseases, such as hypertension and hypercholesterolemia [7].

Watermelon (Citrullus lanatus L.) is a widely popular fruit used across the world for its numerous nutritional and health-promoting benefits. Watermelon has traditionally been used to help treat a diverse range of diseases in Africa and Asia, including erectile dysfunction, dehydration, and renal disease [8]. Watermelon seeds have great nutritional value due to their high protein, oil, citrulline, carotenoids, and lycopene content, and as a strong source of vitamin C, niacin, folate, and dietary fiber [9]. The large majority of research studies on watermelon's health benefits have concentrated on the juice [10], but the seeds have also attracted significant attention in recent years [11]. Citrullus lanatus seed extracts have also been shown to have antihyperglycemic and hypolipidemic potential in diabetic rats [12]. In addition, seed extracts have been demonstrated to protect against aspartame-induced oxidative stress [13]. There is presently no research showing that WSO can protect rats from diazinon-induced liver and kidney damage. As a result, the study aimed to examine the protective potential of watermelon seed oil alone or mixed with pumpkin seed oil against hepatorenal toxicity induced by long-term diazinon administration in rats.

## Material and Methods

### *Chemicals*

Diazinon (O, O-Diethyl O-[4-methyl-6-(propane-2-yl)pyrimidin-2-yl] phosphorothioate; purity 100%) was purchased from Sigma-Aldrich (St. Louis, MO, USA). All other reagents were commercial products of standard chemical grade. Pumpkin seed oil was purchased from Now Foods Co., Bloomingdale, IL., USA. Watermelon seed oil was purchased from Sweet Essential, imported from Egypt.

### *Experimental Animals and Design*

Adult male albino rats (Sprague-Dawley) were used in this study, initially weighing 136±5 g. Rats were divided and housed in environmentally controlled cages (22±1 0C, 50±5% humidity, and 12 h light/dark cycle). Rats were fed a balanced standard diet and allowed water ad libitum throughout the whole experiment (35 days).

The study was conducted between May 2024 and July 2024 at Central Laboratory Unit - Ain Shams University. Fifty male rats were classified into five groups (10 rats/group) as follows:

Group 1 (Control): Rats were untreated and received the standard diet.

Group 2 (diazinon intoxicated group- DZN): Rats were orally administrated with 50 mg/kg body weight of DZN in corn oil by gastric tube daily for 5 weeks.

Group 3 (pumpkin seed oil group- PSO + DZN): Rats received the standard diet with pumpkin seed oil at a dose of 1.5 ml/kg b.w/ day orally by gastric tube and after six h exposed to DZN at the same dose given to group 2, daily for 5 weeks.

Group 4 (watermelon seed oil group-WSO+DZN): Rats received the standard diet with watermelon seed oil at a dose of 1.5 ml/ kg b.w./ day orally by gastric tube and after six h exposed to DZN at the same dose given to group 2, daily for 5 weeks.

Group 5 (PSO+ WSO+ DZN group): Rats received the standard diet with pumpkin seed oil and watermelon seed oil at the same dose given to groups 3 and 4, respectively, and after six h exposed to DZN at the same dose given to group 2, daily for 5 weeks.

### *Analytical Procedures*

On the last day of the experimental period, rats were fasted overnight and then anesthetized with ether, blood samples were drawn from the hepatic portal vein and then transported into centrifuge tubes. Tubes were centrifuged at 5000 x g for 15 minutes at 23°C to collect serum for the biochemical examination. Serum samples were stored at -20°C until used for various biochemical analyses. To determine hematological parameters, additional blood samples (approximately 1 ml) were collected into test tubes containing EDTA.

The kits of urea, creatinine, total proteins, total bilirubin, Cystatin-C, neutrophil gelatinase-associated lipocalin (NGAL), total antioxidant capacity (TAC), superoxide dismutase (SOD), malondialdehyde (MDA), and reduced glutathione (GSH) were obtained from Bio diagnostics Co. (Cairo, Egypt). Meanwhile, nuclear factor kappa-B (NF-κB), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) were determined using enzyme-linked immunosorbent assay kits (ELISA) according to the manufacturer Kamiya Biomedical Co. (CA, USA). Alanine transaminase (ALT), aspartate transaminase (AST), paraoxonase-1 (PON1), and gamma-glutamyl transferase (GGT) activities were determined using commercial kits (Biovision, CA, USA). Platelet counts were evaluated using a hematology analyzer (Beckman Coulter, USA).

Prothrombin time (PT) measurement: PT is measured by Quick's method. The reagent used in PT testing is thromboplastin. The time in seconds taken for the formation of a fibrin clot is

measured as PT.

*Statistical Analysis*

Statistical significance tests were performed using SPSS (v.24, IBM SPSS Statistics, US) at p≤0.01 using one-way analysis of variance (ANOVA) followed by LSD post hoc multiple comparisons. All data were expressed as mean ± SE for ten rats of each group using Microsoft Excel.

*Ethical Approval*

This study was approved by the Ethics Committee of Ain Shams University (Date: 2024-04-01, No: sci1432409001).

## Results

Results presented in Table 1 revealed that administration of diazinon results in an increase (p≤0.01) in values of ALT, AST, GGT, and PON1 compared with untreated control rats. The administration of PSO and WSO reduced these levels significantly (p≤0.01) and reduced them to nearly control levels. Diazinon exposure was associated with hepatotoxicity in male rats, as revealed by a decrease in total proteins and an increase in serum levels of total bilirubin. An improvement was detected following treatment with PSO combined with WSO. Results revealed a correlation between DZN-induced hepatotoxicity and the increased time of prothrombin (by 58.5%) and reduced platelets count (by -52.5%). Treatment with PSO and WSO caused an increase in platelet count and significantly improved the prothrombin time (Table 2). Rats who received DZN demonstrated a significant reduction in SOD, GSH, and TAC levels (by -48.0 %, -61.9 %, and -60.0 % for SOD, GSH, and TAC respectively, as compared to the control group (P ≤ 0.01). On the other hand, the serum level of MDA was higher in the DZN-intoxicated group (by 72.5 % as compared with the control group. WSO or PSO effectively reversed these effects during oxidant damage. Treatment with PSO maintained TAC and GSH levels higher than WSO (Figure 1). Diazinon exposure induced nephrotoxicity, which is displayed by significant changes in biomarkers of serum kidney function values. DZN increased urea, cystatin C, NGAL, and creatinine as compared to the normal control group. These effects were pronouncedly alleviated by treatment with PSO (by -22.0%, -35.49%, -55.7%, and -48.7% for NGAL, cystatin C, urea, and creatinine, respectively) compared with the DZN group. The nephroprotective effect was more apparent when WSO was administered in combined with PSO as a protective agents (by -34.6%, -47.4%, -57.9%, and -66.6%, for NGAL, cystatin C, urea. and creatinine respectively) compared with the DZN group. (Table 3). Treatment with PSO (G3) and WSO (G4) caused a significant reduction in inflammatory biomarker levels when compared to the DZN-intoxicated group. Results revealed a correlation between DZN-induced nephrotoxicity and the elevated serum levels of CRP and TNF-α, thus indicating toxicity of renal cells. An improvement of these biomarker levels was detected following treatment with PSO mixed with WSO (Figure 2).

**Table 1.** Effect of various treatments on serum ALT, AST, GGT, and PON1 activities

| Groups | ALT (U/L) | AST (U/L) | GGT (IU/L) | PON1 (U/ml) |
|---|---|---|---|---|
| Control | 27.2 $^{a}$ ± 1.8 | 36.9 $^{a}$ ± 1.10 | 24.7 $^{a}$ ± 1.2 | 162.15 $^{a}$ ±9.11 |
| DZN | 101.50 $^{b}$ ± 3.0 | 82.60 $^{b}$ ± 3.2 | 66.3 $^{b}$ ± 1.9 | 295.00 $^{b}$ ±11.32 |
| DZN+ PSO | 52.55 $^{c}$ ± 1.40 | 49.50 $^{c}$ ± 2.5 | 42.2 $^{c}$ ± 1.5 | 232.30 $^{c}$ ±8.33 |
| DZN+ WSO | 61.80 $^{d}$ ± 1.75 | 56.90 $^{d}$ ± 1.5 | 47.5 $^{d}$ ± 1.0 | 240.11 $^{c}$ ±10.05 |
| DZN+ PSO+ WSO | 41.33 $^{e}$ ± 1.65 | 38.25 $^{a}$ ± 1.3 | 36.5 $^{e}$ ± 2.3 | 222.75 $^{d}$ ±10.1 |

Data are expressed as mean+/- SE, (n= 10). This means that bearing different letters (a, b, c, d, e) in the same column are significantly at (p≤0.01). DZN: diazinon; PSO: pumpkin seed oil; WSO: watermelon seed oil

**Table 2.** Effect of various treatments on prothrombin time, platelets counts and serum levels of total proteins, and total bilirubin

| Groups | Total Protein (g/dl) | Total Bilirubin (µmol/L) | Prothrombin Time (Sec.) | Platelets count (x109/ L) |
|---|---|---|---|---|
| Control | 7.55 $^{a}$ ±0.82 | 12.35 $^{a}$ ± 0.80 | 12.3 $^{a}$ ± 0.50 | 292.0 $^{a}$ ±12.2 |
| DZN | 3.66 $^{b}$ ±0.35 | 26.60 $^{b}$ ± 1.50 | 19.5 $^{b}$ ± 0.3 | 138.7 $^{b}$ ±9.60 |
| DZN+ PSO | 5.52 $^{c}$ ±0.75 | 18.35 $^{c}$ ± 1.10 | 13.1 $^{c}$ ± 0.1 | 278.5 $^{c}$ ±10.3 |
| DZN+ WSO | 5.11 $^{c}$ ±0.95 | 15.00 $^{d}$ ± 1.05 | 15.2 $^{d}$ ± 0.1 | 270.1 $^{c}$ ±9.5 |
| DZN+ PSO+ WSO | 6.95 $^{a}$ ±0.75 | 16.35 $^{e}$ ± 0.95 | 13.0 $^{c}$ ± 0.2 | 306.1 $^{a}$ ±14.5 |

Data are expressed as mean+/- SE, (n= 10). This means that bearing different letters (a, b, c, d, e) in the same column are significantly at (p≤0.01). DZN: Diazinon; PSO: pumpkin seed oil; WSO: watermelon seed oil

**Table 3.** Effect of all treatments on serum levels of NGAL, Cystatin C, Urea, and Creatinine

| Groups | NGAL (ng/ml) | Cystatin C (ng/ml) | Urea (mmol/L) | Creatinine (mg/dL) |
|---|---|---|---|---|
| Control | 73.22 a ±3.20 | 75.3 a ±1.3 | 3.25 a ± 0. 20 | 0.55 a ± 0.07 |
| DZN | 126.80 b ±6.5 | 168.2 b ±4.0 | 11.30 b± 0.35 | 1.95 b ± 0.05 |
| DZN+ PSO | 98.90 c ±9.2 | 108.5 c ±2.5 | 5.00 c ± 0.15 | 1.00 c ± 0.07 |
| DZN+ WSO | 101.30 c ±5.5 | 113.7 c ±6.3 | 7.25 d ± 0. 16 | 1.20 c ±0.09 |
| DZN+ PSO+ WSO | 82.90 d ±9.0 | 88.4 d ±2.9 | 4.75 e ± 0.35 | 0.65 a ± 0.05 |

Data are expressed as mean+/- SE, (n= 10). This means that bearing different letters (a, b, c, d, e) in the same column are significantly at (p≤0.01). DZN: diazinon; PSO: pumpkin seed oil; WSO: watermelon seed oil

## Discussion

Diazinon (DZN) is an insecticide extensively used to control pests in crops and animals. However, its indiscriminate use may lead to liver and kidney damage in animals and humans. The present study was designed to evaluate whether pre-treatment with PSO and WSO would have protective influences on DZN-induced hepatorenal injury in male rats.

The results of the current study demonstrated a significant increase in serum levels of AST, ALT, and GGT activities in DZN-treated rats. The increases in enzyme activities may be owing to hepatic cell damage or dysfunction, which results in the leakage of these enzymes from hepatocytes into the blood and/or to the disturbance in the balance between biosynthesis and degradation. Meanwhile, DZN treatment also caused a significant increase in serum bilirubin levels, arising from the toxic effect of DZN by destroying red blood cells. However, serum bilirubin increases could also be of hepatic origin [14]. The administration of PSO and WSO reduced these levels significantly (p≤0.01) and reduced them to nearly control levels. An improvement was detected following treatment with PSO mixed with WSO. A possible explanation is that PSO had hepatoprotective effects on DZN toxicity by scavenging free radicals, reducing their damaging effects, and remedying liver

injury.

Studies have revealed that oxidative stress can be an important component of the mechanism of DZN intoxication. Treatment of rats with DZN significantly promotes a decrease in the level of GSH, events that may be related to the renal toxicity of DZN mediated by oxidative stress. The present results showed that the administration of DZN caused significant decreases in levels of serum GSH, TAC, and SOD, while the level of serum MDA was significantly increased. These findings are consistent with previous investigations, which indicated that DZN and other pesticides [15].

The results of the current study showed that PSO effectively reversed these effects during oxidant damage. Pumpkin seed oil can play a major role in protecting the liver against alcohol-induced hepatotoxicity and oxidative stress. Pre-treatment with PSO showed hepatoprotective effects, including antioxidant protection and enhanced detoxification [24]. Treatment with PSO counteracts oxidative parameters. The strong antioxidant activity of constituents of pumpkin led to an effective protection of the mitochondrial membrane, as underscored by a significant decline in MDA value. These were in line with Eraslan et al. [16], where PSO led to biochemical alterations in the antioxidant enzyme action due to its potential to eliminate reactive oxygen species produced under normal conditions.

Another study by Xu [17] found that polysaccharides from pumpkin may increase the activity of GSH-Px while decreasing serum MDA content in mice tumors due to its high vitamin A and

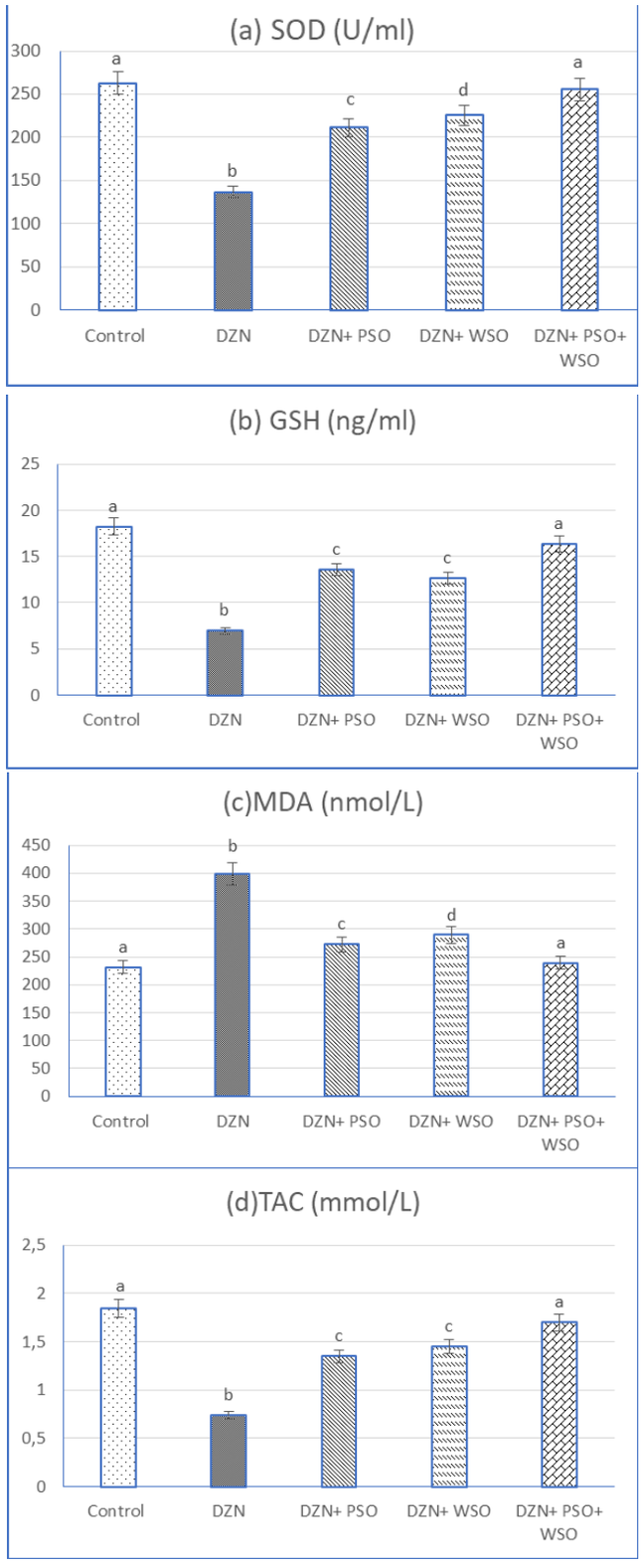


**Figure 1.** Effect of all treatments on serum levels of oxidative stress biomarkers. The P values were calculated using the One-Way ANOVA test. This means that bearing different letters (a, b, c, d, e) are significantly at (p≤0.01. The abbreviations mean DZN: diazinon; PSO: pumpkin seed oil; WSO: watermelon seed oil

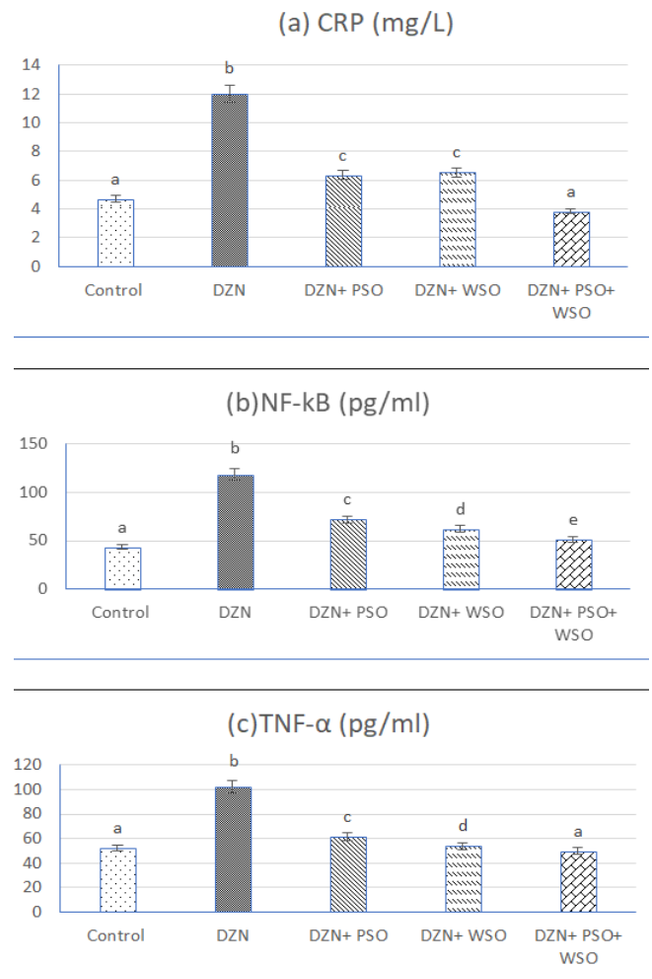


**Figure 2.** Effect of all treatments on serum levels of inflammatory biomarkers. The P values were calculated using the One-Way ANOVA test. This means that bearing different letters (a, b, c, d, e) are significantly at (p≤0.01. The abbreviations mean. DZN: diazinon; PSO: pumpkin seed oil; WSO: watermelon seed oil

tannin content, particularly present in the oil, which possesses antioxidant activity. Vitamin E and tocopherols prevent damage caused by free radicals; suppressed lipid peroxidation enhances GSH activity and improves membrane integrity.

Que et al. [18] have reported that PSO is rich in phenolic and flavonoid compounds. These components are said to possess many functional groups, including hydroxyl groups, which have very strong antioxidant potential. Polyphenols and flavonoids can scavenge hydroxyl radicals and superoxide radicals. This is why pumpkin is a plant that has been frequently used as a functional food or medicine. In addition, PSO supplementation ameliorated the non-enzymatic GSH and the enzymatic antioxidant activities of SOD. This rebalance of the antioxidant status is certainly related to the high antioxidant potential of PSO, which contains polyphenols, flavonoids, acids, and tannins detected in its phytochemical study. The PSO is also known to contain high amounts of tocopherols and selenium, which are powerful antioxidants [19]. In the same way, the pre-treatment of rats with pumpkin seed oil induced a noticeable reduction in lipid peroxidation and boosted the antioxidant status represented by hepatic TAC and GSH.

The present results demonstrated that the treatment of rats with watermelon seed oil improved the biochemical alterations induced by DZN intoxication. This indicated the effectiveness of WSO in the prevention of DZN toxicity. The possible mechanism of WSO as a protective factor may be due to its antioxidant effects, which impair the activation of DZN into the reactive form. Dietary intake of antioxidants can inhibit or delay the oxidation of susceptible cellular substrates to prevent oxidative stress [20].

Watermelon seed oil significantly ($p \leq 0.01$) reduced MDA levels while SOD activity and TAC increased in all treated groups (G4, G5). The antioxidant properties of WSO could be attributed to the presence of flavonoids, predominantly catechin, alkaloids, oxalates, and saponin in WSO. Flavonoids have been reported to act as powerful antioxidants that can protect the human body from free radicals and reactive oxygen species [21].

In response to inflammation and cell damage, the serum level of C-reactive protein (CRP) rapidly and significantly increases. CRP could be involved in the regulation of renal function. TNF-α and NF-κB levels were raised in DZN-induced rats in response to these pro-inflammatory cytokines, which in turn raised CRP levels. The antioxidants and anti-inflammatory potential of the Citrullus lanatus seeds were investigated by Logaraj [22], who confirmed that watermelon seeds are a good source of linoleic acid (18:2 ω-6) as a major fatty acid.

The results of the present study showed that WSO lowered the serum CRP level because of its confirmed anti-inflammatory effect, and this was due to the presence of established polyphenolic compounds such as tannin and flavonoids. Flavonoids like fisetin and quercetin have been shown to activate NF-κB. The activation of NF-κB is critical for the production of pro-inflammatory cytokines [23].

The goal of the current study was to determine if the flavonoid extract from Citrullus lanatus seed might protect against diazinon-induced kidney damage. The outcomes of this research indicated that diazinon-induced kidney damage was connected with increased oxidative stress and renal biochemical markers. In the present study, renal dysfunction was detected by significant increases in serum creatinine, NGAL, cystatin C, and urea levels in rats exposed to DZN. The present decreases in total serum proteins and albumin are generally due to the findings of several studies showing increases in these parameters in experimental animals exposed to DZN and other pesticides [24]. An increase in levels of serum creatinine and urea revealed damaged kidney function or kidney disorder. This disorder will cause the creatinine level in the blood to rise due to the inability of the kidneys to clear creatinine [25]. Treatment with WSO significantly ($p \leq 0.01$) reduced urea and creatinine concentrations when compared to the DZN-intoxicated group (G2). The significant decrease in creatinine concentration after treatment may be due to the strength of the WSO to ameliorate kidneys, thereby stimulating the rate of filtration by kidneys.

According to the authors` knowledge, there is no previous studies have investigated the valuable effect of pumpkin seed oil mixed with watermelon seed oil for prevention and/or reduction of toxicity induced by diazinon.

### *Limitations of the study*

The most significant limitation of this study is the lack of previous research studies on the topic and time constraints.

### *Conclusion*

Based on the present study, it can be concluded that pumpkin seed oil and watermelon seed oil improve the hepatorenal alterations induced by DZN intoxication. Moreover, the most protective effects were observed in rats treated with PSO mixed with WSO. Additionally, the antioxidant properties of these oils support the bioactive roles of their protective effects on DZN toxicity. To strengthen these findings, further experimental studies are needed to evaluate the effect of different doses of these oils as protective factors against the toxicity of DZN.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and Human Rights Statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.*

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***Conflict of Interest***

*The authors declare that there is no conflict of interest.*

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